



Detailed Subphenotyping of Lumbar Modic Changes and Their Association with Low Back Pain in a Large Population-Based Study: The Wakayama Spine Study

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ABSTRACT

Introduction: To examine the association between the five types of Modic changes and

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low back pain (LBP) in a large population-based cohort.

Methods: Of the 952 participants in the second Wakayama Spine Study, 814 (men, 246; women, 568; mean age, 63.6 years) were included in this study. Endplate changes on magnetic resonance imaging were classified according to the Modic classification system. Low back pain (LBP) was defined as continuous back pain for at least 48 h in the past month that is currently present. The prevalence of Modic changes in the lumbar region was assessed. Multivariate logistic regression analysis was conducted to determine the association between detailed subphenotype of Modic change and LBP comparing no Modic change in the lumbar spine and each level, respectively.

Results: Modic changes throughout the lumbar spine were noted in 63.5% ($n = 516$) of all participants, with types I, I/II, II, II/III, and III observed in 7.8% ($n = 63$), 10.8% ($n = 88$), 40.0% ($n = 326$), 2.1% ($n = 17$), and 2.7% ($n = 22$), respectively. Modic types I/II were associated with LBP [odds ratio (OR): 3.26; 95% confidence interval (CI) 1.9, 5.5]. Furthermore, Modic type I/II changes at L2/3 and L4/5 were significantly associated with LBP (odds ratio: 2.77; 95% CI 1.04, 7.39 at L2/3; odds ratio: 2.86; 95% CI 1.39, 5.90 at L4/5).

Conclusions: Type I/II Modic changes in the lumbar region are significantly associated with LBP. To the best of our knowledge, this is the first large population-based study on the

association between various Modic changes and LBP.

Keywords: Modic change; Detailed subphenotyping; Low back pain; Large population-based study

Key Summary Points

Why carry out this study?

Low back pain causes functional impairment, diminished quality of life, work disability, potential psychological distress, and increased healthcare costs.

Lumbar phenotypes as detailed subphenotyping of lumbar Modic change become pain generators.

What was learned from the study?

Type I/II Modic changes in the lumbar region are significantly associated with low back pain.

Modic changes can be a clinically relevant imaging phenotype. These results underscore the importance of continued investigation of the molecular pathogenesis and genetics underlying Modic changes and the development of predictive models.

INTRODUCTION

Low back pain (LBP) leads to functional impairment, decreased quality of life, disability in the workplace, potential psychological distress, and increased health care costs [1–3]. A useful tool to identify the potential source of LBP and help inform management is magnetic resonance imaging (MRI) of the lumbar spine [4, 5]. However, we often have a gap between the clinical profile and MRI findings [6, 7]. Moreover, inappropriate decision-making based on a lack of recognizing of lumbar MRI phenotypes [e.g., black disc, endplate abnormalities,

Modic changes, and high-intensity zones (HIZ)] might explain the relatively high incidence of failed spinal surgeries and poor patient outcomes with LBP [5–8]. Such lumbar phenotypes have been reported to interact with pain pathways or become the pain generators, suggesting that they can be novel factors that can guide clinical decision-making, thereby further underscoring the importance of imaging phenotype profiling [8–13].

The Modic classification was introduced in 1988 [14]. According to this classification, type I represents bone marrow edema and inflammation, type II is associated with conversion of normal red hematopoietic bone marrow into yellow fatty marrow as a result of ischemia [14], and type III is thought to represent subchondral bone sclerosis [51]. Some have proposed this classification as a diagnostic biomarker for LBP based on small studies, while others did not find similar associations [14–27]. The association of Modic change with LBP has been verified in several diverse populations [10–12, 24]. Furthermore, most previous studies have found a closer association between LBP and Modic type I, in particular [15–17, 22, 23, 25–27], yet others showed no association between Modic change and LBP [28, 29].

In longitudinal studies, mixed Modic changes (type I/II and type II/III) have also been identified in the previous studies [14, 15]. Modic et al. showed that type I changes commonly progress to type II changes, but they can also revert back to normal [14]. Braithwaite et al. suggested that Modic changes can convert from one type to another and that they all present different stages of the same pathologic process [15].

When different types, usually I and II or II and III, are observed at the same adjacent vertebral body, they are termed mixed types (I/II or II/III, respectively) [11, 15, 16, 18]. However, several previous studies considered that type I Modic change including type I/II represents an active inflammatory process; therefore, these previous studies classified type I and type I/II as “type I” group in the analyses [10–12, 14, 20–22]. Similarly, previous studies had classified type II and type II/III as “type II” group [10–12, 14, 20–22]. These studies have

had at most moderate sample sizes, and insufficient assessments of spine degenerative phenotypes and confounding factors, such as disc degeneration, HIZ, and disc displacement, were not considered [14–21].

To the best of our knowledge, no population-based study has separately examined the association of type I, type I/II, type II, type II/III, and type III with the presence and intensity of LBP.

The objectives of this study were to examine the prevalence of the five types of Modic change throughout the lumbar spine and to clarify the associations between LBP presence and intensity and each type of Modic change in a large population.

METHODS

Study Population and Design

The Wakayama Spine Study is a large-scale study of middle-aged and older residents designed to address the etiology of common spinal disorders in Japan [30–33]. Our study population was a sub-cohort of Research on Osteoarthritis/Osteoporosis Against Disability (ROAD). The ROAD study was a prospective study of bone and joint diseases consisting of middle-aged and older residents established in three communities in Japan [34–37]. The participants in the ROAD study were recruited from listings of resident registrations in three communities that have different characteristics based on their geographical setting: an urban setting, “town I” in Tokyo; a mountainous setting, “town H” in Wakayama; and a coastal setting, “town T” in Wakayama. The Wakayama Spine Study started in the mountainous town H and coastal town T in Wakayama in 2008 [30–32]. In the current study, the participants were residents of town T who were at least 20 years of age, of either sex, and willing to respond to a survey distributed in 2013 as the second Wakayama Spine Study [33].

The inclusion criteria were the ability to walk to the survey site, report data, and sign an informed consent form. Individuals with spinal tumors, infections, chronic inflammatory conditions, previous posterior spinal fusion surgery,

contraindications to MRI (e.g., pacemakers), and/or other disqualifiers (e.g., pregnancy) were excluded. In total, 857 individuals underwent MRI of the lumbar spine. However, the MRI results were not available for 43 individuals because of incomplete T1-weighted (T1W) and T2-weighted (T2W) sagittal lumbar images or insufficient image quality for Modic change assessment. Therefore, 814 individuals were included in this study. The study was approved by the institutional ethics committees of the University of Tokyo (nos. 1264 and 1326) and Wakayama Medical University (no. 373). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All participants provided their written informed consent.

LBP and LBP Intensity

All participants were also asked by experienced orthopedic surgeons about LBP: “Have you experienced continuous LBP for at least 48 h on most days during the past month, in addition to now?” Those who answered “yes” were defined as having LBP, in accordance with previous studies [36, 37, 53]. Separately, LBP intensity was assessed using the visual analog scale (VAS) score (with 0 representing no pain and 100 mm representing the worst pain ever experienced) to all participants.

MRI Protocol

Lumbar MRI was performed using a mobile unit (Achieva 1.5 T; Philips Medical Systems, Best, The Netherlands) for all participants. Lumbar MRI was performed for all participants on the same day as the questionnaire and anthropometric examination. All participants underwent lumbar supine position MRI. The imaging protocol was sagittal T2W fast-spin echo (FSE), with a repetition time (TR) of 3000 ms/echo and an echo time (TE) of 120 ms. The field of view (FOV) was 270 × 270 mm. The sagittal T1W FSE was performed with a TR of 540 ms/echo, a TE

of 10 ms, and an FOV of 270×270 mm. All sections were 5 mm thick, and 11 total slices were available.

Evaluation of MRI Results

Modic change was defined as $> 50\%$ of the width and $> 25\%$ of the height of the vertebral body areas of hypointense and hyperintense signal changes along the endplates, tending to be linear and always parallel to the vertebral endplates on sagittal T1W and T2W images as well as previous reports [20, 52]. We defined hypointense signal as appreciably of similar brightness as the cerebrospinal fluid signal of the same level on T1W images and hyperintense signal as appreciably of similar brightness as the cerebrospinal fluid signal of the same level on T2W image. Modic type I was defined as diffuse hypointense signal on T1W and hyperintense signal on T2W. Type I/II was defined as mixed hypointense signals surrounding hypointense signals on T1W and mixed hyperintense signals surrounding hypointense signal on T2W. Type II was defined as diffuse hyperintense signals on both T1W and T2W. Type II/III was defined as mixed hypointense surrounding hyperintense signals on T1W and mixed hypointense surrounding hyperintense signals on T2W. Finally, type III was defined as diffused hypointense signals on both T1W and T2W (Fig. 1).

To evaluate intra- and interobserver reliability, two orthopedic surgeons evaluated the MR images in the same manner. Kappa > 0.90 was considered excellent, 0.80 – 0.90 good, 0.60 – 0.80 fair, and < 0.60 poor [38, 49]. The kappa coefficients for intra- and interobserver variability of Modic type were 0.86 and 0.82 , respectively. Modic types were assessed by a board-certified orthopedic surgeon (MT) who was blinded to the participants' information. Intra- and interobserver reliability of Modic type determination was assessed. The reliability of other MRI phenotypes has been reported elsewhere as good to excellent [38, 49]. Two separate sets of 50 randomly selected MRIs were assessed by two readers (MT and HT) to determine intra- and interobserver reliability in evaluating Modic changes. The assessments were performed

independently more than 1 month apart, and the readers were blinded to the participants' information. The kappa coefficients were 0.99 and 0.83 [95% confidence interval (CI) MT, 0.98 , 0.99 ; HT: 0.73 , 0.91 ; $p < 0.001$], respectively, for intraobserver reliability and 0.94 (95% CI 0.88 , 0.96 ; $p < 0.001$) for interobserver reliability. Any disagreements in classification were settled by consensus after reliability assessments were completed as well as previous report [8–10, 13, 30–33, 38, 49].

Disc degeneration (DD) was evaluated using the Pfirrmann classification, ranging in scores from 1 (normal) to 5 (most severe) for each disc [39]. At least one \geq grade 4 DD in the lumbar region was defined as the presence of DD. Bright white signal located in the substance of the annulus fibrosus defined HIZ, clearly dissociated from the signal of the nucleus pulposus, which was surrounded by a low-intensity (black) signal of the annulus fibrosus, and was appreciably brighter than the cerebrospinal fluid signal at the same level on T2W sagittal MR images of L1–S1 [8, 33, 40]. At least one HIZ in the lumbar region defined the presence of HIZ. Disc displacement was evaluated as a disk bulge, protrusion, or extrusion [8, 12, 33]. At least one disc displacement in the lumbar region defined the presence of disc displacement.

Statistical Analyses

All statistical analyses were performed using JMP version 14 (SAS Institute Japan, Tokyo, Japan). The prevalence of Modic types was examined per subject and per disc level. Presence of a Modic change was defined as having at least one Modic change in the lumbar region. Moreover, we assessed the prevalence of Modic type in the lumbar spine and at each lumbar disc level. Analysis of variance (ANOVA) was used to assess the association between LBP VAS score and Modic types I, type I/II, type II, type II/III, type III, and no Modic changes because each subject provided only one observation in this analysis; therefore, we used the ANOVA assumption of independence observation. First, multivariate logistic regression models were used to evaluate the association between each

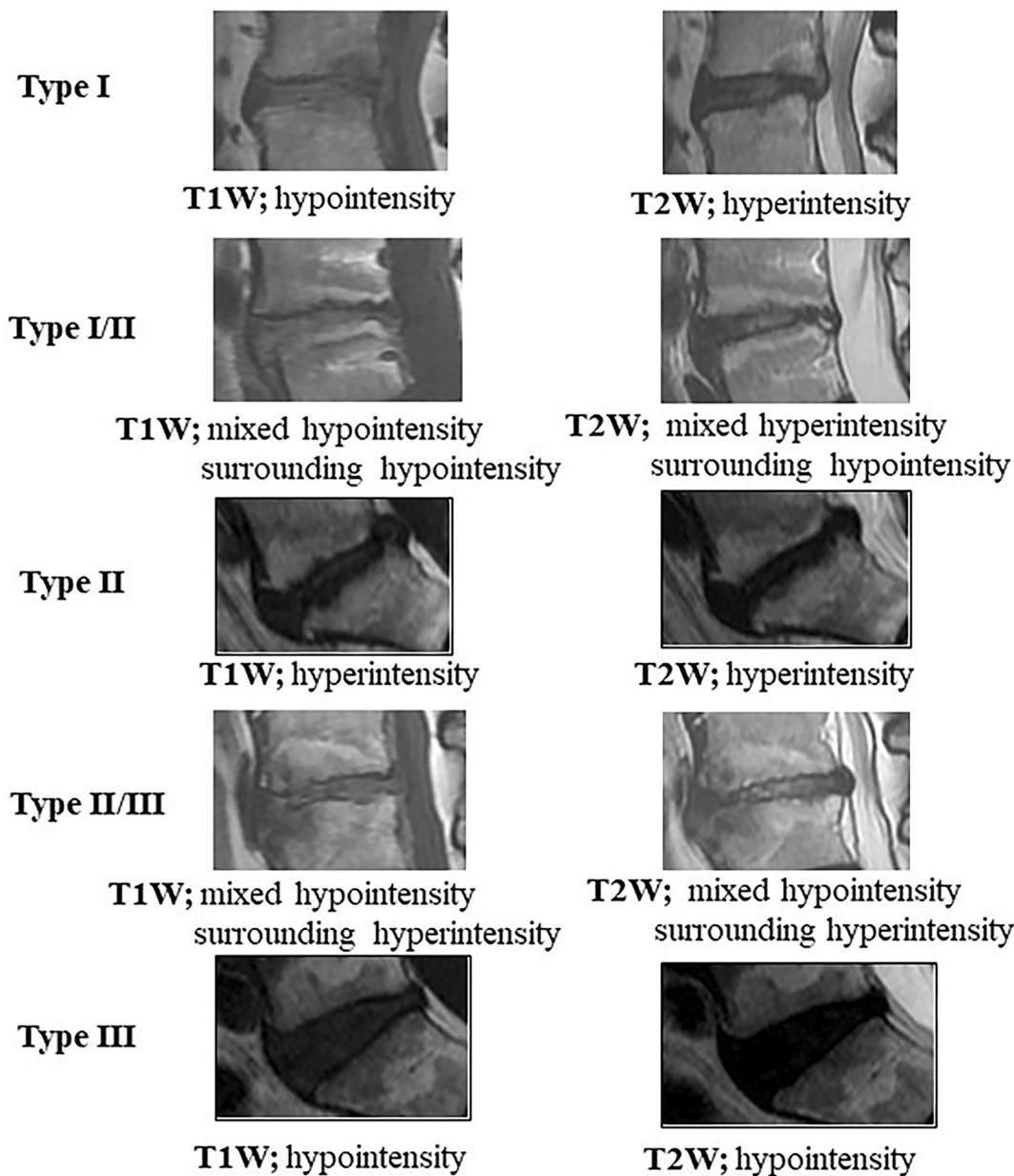


Fig. 1 Modic type I was defined as diffuse hypointense signal on T1W and hyperintense signal on T2W. Type I/II was defined as mixed hypointense signals surrounding hypointense signals on T1W and mixed hyperintense signals surrounding hypointense signal on T2W. Type II was defined as diffuse hyperintense signals on both T1W

and T2W. Type II/III was defined as mixed hypointense surrounding hyperintense signals on T1W and mixed hypointense surrounding hyperintense signals on T2W. Finally, type III was defined as diffused hypointense signals on both T1W and T2W

of Modic type I, type I/II, type II, type II/III, and type III as independent variables, and the presence of LBP as dependent variable, compared with no Modic change, after adjustment for age,

sex, body mass index (BMI), presence of DD, presence of HIZ, and presence of disc displacement as previously defined [14–17, 20]. Because the previous studies reported the significant

association among BMI, presence of DD, presence of HIZ, and presence of displacement and LBP, we selected these independent variables as the confounding factors in this study [14–17, 20, 30, 32]. The threshold for statistical significance was set at $p < 0.05$, and the corresponding 95% CIs were assessed.

RESULTS

Study Population Characteristics

Eight hundred fourteen individuals underwent lumbar MRI assessment, of whom 246 were men (30.2%) and 568 women (69.8%). The mean age across the entire cohort was 63.6 [standard deviation (SD): ± 13.1] years. The mean age of the men and women was 63.1 (SD: ± 14.0) and 63.8 (SD: ± 12.7) years, respectively. The mean height was 166.8 (SD: ± 6.7) cm in men and 153.3 (SD: ± 6.4) cm in women. The mean weight was 66.8 (SD: ± 11.0) kg in men and

53.1 (SD: ± 9.0) kg in women. The mean BMI was 24.0 (SD: ± 3.6) kg/m² in men and 22.6 (SD: ± 3.6) kg/m² in women. The prevalence of LBP was 30.9% in men and 31.5% in women, respectively, and the corresponding VAS score was 12.4 ± 20.8 in men and 14.3 ± 22.9 women, respectively (Table 1).

Prevalence of Modic Changes

Modic changes anywhere in the lumbar spine were noted in 63.5% ($n = 516$) of all participants, within which the prevalence of Modic types I, I/II, II, II/III, and III was 7.8% ($n = 63$), 10.8% ($n = 88$), 40.0% ($n = 326$), 2.1% ($n = 17$), and 2.7% ($n = 22$), respectively. Among participants exhibiting Modic changes, 37.2% had a single Modic change ($n = 192$), 25.1% had 2 ($n = 130$), 16.1% had 3 ($n = 83$), 11.2% had 4 ($n = 58$), and 10.4% had 5 ($n = 54$). Table 2 shows the distribution of Modic types across the lumbar levels, with L5/S1 showing the highest

Table 1 Characteristics of participants

| | Overall | Male | Female |
|------------------------------------|-----------------|-----------------|-----------------|
| No. of participants | 814 | 246 | 568 |
| Age, years | 66.4 \pm 13.5 | 63.1 \pm 14.0 | 63.8 \pm 12.7 |
| Height, cm | 157.4 \pm 8.9 | 166.8 \pm 6.7 | 153.3 \pm 6.4 |
| Weight, kg | 57.2 \pm 11.5 | 66.8 \pm 11.0 | 53.1 \pm 9.0 |
| Body mass index, kg/m ² | 23.0 \pm 3.7 | 24.0 \pm 3.6 | 22.6 \pm 3.7 |
| Radiographic | | | |
| Modic change (%) | 516 (63.4%) | 168 (68.3%) | 348 (61.3%) |
| Disc degeneration (%) | 746 (91.6%) | 225 (91.5%) | 521 (91.7%) |
| HIZ (%) | 310 (38.1%) | 101 (41.4%) | 209 (36.8%) |
| Disc displacement (%) | 550 (67.6%) | 176 (71.5%) | 374 (65.8%) |
| Symptoms | | | |
| Low back pain (%) | 255 (31.3%) | 76 (30.9%) | 179 (31.5%) |
| Low back pain VAS | 13.7 \pm 22.3 | 12.4 \pm 20.8 | 14.3 \pm 22.9 |

Non-paired *t*-test was used to determine differences in demographic characteristics and symptom between males and females. Values are the means \pm standard deviation

VAS visual analog scale

Table 2 Distribution of Modic types in the entire lumbar spine and at each lumbar level (*n*: 814 subjects)

| Disc level | None, <i>n</i> (%) | Type I, <i>n</i> (%) | Type I/II, <i>n</i> (%) | Type II, <i>n</i> (%) | Type II/III, <i>n</i> (%) | Type III, <i>n</i> (%) |
|---------------------|-----------------------|-------------------------|----------------------------|--------------------------|------------------------------|---------------------------|
| L1/L2 | 674 (82.8) | 7 (0.9) | 4 (0.5) | 110 (13.5) | 4 (0.5) | 15 (1.8) |
| L2/L3 | 598 (73.5) | 16 (0.2) | 20 (2.5) | 157 (19.3) | 6 (0.7) | 17 (2.1) |
| L3/L4 | 581 (71.3) | 18 (2.2) | 21 (2.6) | 163 (20.0) | 6 (0.7) | 25 (3.1) |
| L4/L5 | 534 (65.6) | 32 (3.9) | 37 (4.5) | 184 (22.6) | 5 (0.6) | 22 (2.7) |
| L5/S1 | 480 (59.0) | 14 (1.7) | 31 (3.8) | 258 (31.7) | 8 (1.0) | 23 (2.8) |
| Entire lumbar spine | 298 (36.6) | 63 (7.8) | 88 (10.8) | 326 (40.0) | 17 (2.1) | 22 (2.7) |

Every disc level from L1/L2 to L5/S1 has been individually evaluated

prevalence of Modic changes followed by L4/5 and L3/4. However, L4/5, followed by L3/4, showed the highest rates of type I and I/II changes [type I: 3.9% (*n* = 32), type I/II: 4.5% (*n* = 37) at L4/5].

Association Between Modic Types and LBP

The presence of Modic type I/II changes was associated with LBP (odds ratio: 3.26; 95% CI 1.9, 5.5), while that of type I, type II, type II/III, and type III was not, respectively (Table 3). The multivariate analyses showed that type I/II changes at L2/3 and L4/5 were significantly associated with LBP (odds ratio: 2.77; 95% CI 1.04, 7.39 at L2/3; odds ratio: 2.86; 95% CI 1.39, 5.90 at L4/5) (Table 4).

Association Between Modic Types and LBP Intensity

The LBP VAS score was significantly higher in participants with Modic type I and I/II than in those with no Modic changes. The LBP VAS score was 18.4 ± 22.6 mm, 28.90 ± 28.2 mm, 12.3 ± 21.2 mm, 19.2 ± 23.8 mm, 19.2 ± 23.8 mm, and 9.9 ± 19.4 mm in participants with type I, type I/II, type II, type II/III, and type III, and no Modic changes, respectively. Furthermore, the LBP VAS score was significantly higher in patients with type I/II than

Table 3 Multivariate analyses of factors associated with low back pain after adjustment for age, gender, BMI, presence of DD, presence of HIZ, and presence of disc displacement (*n*; 814)

| | OR | 95% CI | <i>p</i> value |
|-------------|--------|---------|----------------|
| Type I | 1.66 | 0.9–3.0 | 0.1 |
| Type I/II | 3.26** | 1.9–5.5 | < 0.0001 |
| Type II | 1.09 | 0.7–1.6 | 0.66 |
| Type II/III | 1.05 | 0.4–3.1 | 0.93 |
| Type III | 1.24 | 0.5–3.2 | 0.66 |

Reference is no Modic change
OR odds ratio, *CI* confidential interval, *BMI* body mass index, *DD* disc degeneration, *HIZ* high-intensity zone
 p* < 0.05; *p* < 0.005

in those with type I (28.0 ± 28.2 vs. 18.4 ± 22.6, *p* < 0.05).

DISCUSSION

To our knowledge, this is the largest study adopting a detailed, systematic, and standardized methodology, to assess the relationship of the five Modic change types with the presence and intensity of LBP. Our large-scale population-based study is the first to note that Modic type I/II change of the lumbar spine is

Table 4 Multivariate analyses of Modic types associated with low back pain in each disc level after adjustment for age, sex, BMI, presence of DD, presence of HIZ, and presence of disc displacement ($n = 814$)

| | L1/2 | | L2/3 | | L3/4 | |
|-----------------|------|-----------|-------|-----------|------|-----------|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| No Modic change | 1 | | 1 | | 1 | |
| Type I | 0.69 | 0.13–3.59 | 1.38 | 0.45–4.24 | 1.95 | 0.74–5.13 |
| Type I/II | 1.44 | 0.18–11.4 | 2.77* | 1.04–7.39 | 1.71 | 0.67–4.38 |
| Type II | 1.09 | 0.69–1.70 | 1.03 | 0.69–1.54 | 1.39 | 0.92–2.1 |
| Type II/III | 1.3 | 0.15–11.2 | 1.56 | 0.29–8.37 | 1.74 | 0.29–10.4 |
| Type III | 1.27 | 0.43–3.77 | 1.34 | 0.48–3.75 | 1.58 | 0.68–3.70 |

| | L4/5 | | L5/S1 | |
|-----------------|--------|-----------|-------|-----------|
| | OR | 95% CI | OR | 95% CI |
| No Modic change | 1 | | 1 | |
| Type I | 1.39 | 0.65–2.98 | 1.26 | 0.38–4.16 |
| Type I/II | 2.86** | 1.39–5.9 | 1.95 | 0.91–4.15 |
| Type II | 1.06 | 0.71–1.57 | 1.06 | 0.75–1.52 |
| Type II/III | – | – | 1.49 | 0.34–6.45 |
| Type III | 1.01 | 0.39–2.62 | 1.25 | 0.48–3.25 |

OR odds ratio, CI confidential interval, BMI body mass index, DD disc degeneration, HIZ high-intensity zones, LBP low back pain
* $p < 0.05$; ** $p < 0.005$

significantly and independently associated with LBP after adjustment for confounding factors. Furthermore, patients with Modic type I/II had higher LBP VAS scores than those with other Modic types.

The prevalence of Modic changes varies from 12 to 62% among patients with LBP, with different rates for each type [10–12, 14–21, 23–29, 41–47]. According to previous studies, type I and type II are the most common patterns observed in the lumbar spine. The inconsistency in results between studies may be due to differences in study design, inclusion criteria, and sample size. However, to our knowledge, no previous studies have conducted this type of detailed investigation in a population-based cohort. Our results showed a similar distribution of Modic changes at L4–L5 or L5–S1 to that reported in previous studies [10–12, 14–21, 23–29, 41–47]. However, the high prevalence of type I/II changes at L4/5 and L5/S is a novel finding.

Three main types of Modic change have been described [10–12, 14–21, 23–29, 41–47]. Modic type I is characterized by hypointensity on T1W and hyperintensity on T2W [14]. It is thought to represent acute inflammatory changes subsequent to degenerative disc disease based on the fibrovascular replacement observed in histopathological specimens of subchondral bone marrow [14, 26, 42]. It has been suggested that Modic type I changes may be a predictor of fast-progressing and deforming disc degeneration [43]. Clinically, it has also been linked to a pattern of inflammatory pain [44]. Modic type II changes appear as hyperintense signals on both T1W and T2W, with yellow marrow replacement observed in histopathological specimens. It could represent a more stable phase of degenerative disc disease, but it does have the potential to convert to another type [23, 45, 46]. Mixed Modic types are thought to develop when one type converts to another [47]. Modic et al. demonstrated that Modic type I changes lead to disruption and fissures of the endplates [14]. If recent microfractures are present, they will show as hypointense signals on T1W and hyperintense signals on T2W. A previous study suggested that Modic type I represents an acute stage, and mixed type I/II may transform to

Type II as the subchondral bone heals [47, 48]. Therefore, we speculate that the acute inflammatory processes occurring in type II changes cause the conversion of yellow marrow to red, with higher LBP intensity resulting in Modic change type I/II.

Differences Between Modic Types I/II and Low Back Pain

The association of Modic changes with LBP has been verified in several diverse patient populations [10–12, 14–21, 23–29, 41–47]. Modic type I has been found to be more closely associated with LBP than other types in several studies [10, 12, 14–29, 42], but there are also studies that show no association between Modic change and LBP [6]. The sample sizes of these studies have usually been limited, and they have not commonly explored the association with severe LBP or disability. One recent population study demonstrated that Modic change is independently associated with episodes of severe and disabling LBP [10]. In the present study, we found an independent association between Modic change type I/II with LBP even after adjustment for confounding factors, including disc degeneration, HIZ, and disc displacement because disc degeneration, HIZ, and displacement were previously reported as factors involved in LBP [4, 5, 7–9, 32]. We also found that the association of type I/II with LBP exhibited a higher odds ratio than other types. Furthermore, the LBP VAS scores were higher in patients with Modic type I/II changes than in those with Modic type I. The current finding of an association between Modic type I/II changes and more severe LBP is a novel finding. To our knowledge, this is the first large study to assess the individual relationships of Modic type I and type I/II with LBP, separately. Ohtori et al. reported that the number of tumor necrosis factor-immunoreactive cells in endplates exhibiting Modic type I changes was significantly higher than that in endplates exhibiting type II changes [22]. However, the number of protein gene product-9.5 and tumor necrosis factor-immunoreactive nerves in endplates exhibiting Modic type II as well as type I was

also higher than that in endplates with no Modic changes. We speculated Modic type I/II was progressed from Modic type I to type II, and the presence of mixed Modic type I/II may involve higher levels of active proinflammatory cytokines due to progress.

Regarding the association between the spinal level exhibiting Modic change and LBP, Kuisma et al. reported that both Modic type I and II lesions at L5–S1, but not at upper levels, are associated with LBP [25]. However, we found that the odds ratio of LBP's association with Modic type I/II lesions at L2/3 and L4/5 was higher than that at L5/S1 after adjustment of disc degeneration, HIZ, and disc displacement. We speculate that the association of LBP symptoms with L2/3 and L4/5 level changes might be due to mechanical factors or other environmental factors, but the precise pathophysiology requires further investigation. Our study sheds much needed light onto the quantitatively detail subphenotyping of Modic change and the clinical profiles. For the first time, we have been able to understand that unique patterns of Modic change may indeed be quantitative pain markers that need further attention and perhaps add to the risk profile of that individual in the development of pain. Furthermore, having this understanding and considering multi-level involvement, we have obtained a much deeper global perspective of that individual.

Limitations

As with any clinical study, there are limitations to ours. This was a cross-sectional study; thus, we cannot definitively conclude the presence of causal relationships. Although our volunteers were recruited from the general population, there are inherent biases and influences with open recruitment. Nevertheless, based on our previous analyses, we have found that our cohort represents a good cross-section of the general population. Furthermore, compared to other population-based studies assessing similar parameters, our study involved a more detailed assessment of our cohort's demographic, lifestyle/environmental, imaging, and clinical

profiles [30–37]. In addition, the ethnic homogeneity of our population would minimize potential ethnicity-related confounders and biases. Nonetheless, future studies are needed to determine whether our results can be generalized to other ethnic groups. We compared the anthropometric data of the present subjects to those reported for the general Japanese population and noted a significant difference in the BMI for men (23.9 ± 3.50 vs. 24.0 ± 3.36 kg/m²; $p = 0.01$) and women (22.6 ± 3.65 vs. 22.3 ± 3.69 kg/m²; $p < 0.05$) for assessing the possibility of sampling-related bias. Therefore, it is likely that the participants had healthier lifestyles than the general Japanese population.

Moreover, we defined cut-off for fatty change in the endplate as appreciably similar brightness as the subcutaneous adipose tissue of the same level on T1W and T2W images.

However, no fat suppression was used in the image acquisition; therefore, we could not differentiate between fatty change and edema in this study. Conclusively, multifactorial factors such as osteoporotic fracture, back muscle strain, and psychosocial problems influence the developmental LBP. Therefore, imaging findings cannot definitively identify the actual source of the LBP. In addition, the definition of LBP is different among various studies [50], and the result of the association between LBP and radiographic change might be changed depending on the definition. Importantly, the large size of the study population and the novel in-depth multiparametric MRI phenotype profiling that could serve as the basis for onward Modic study and phenotype standardization in the future are the strength of our study. Such a foundation can then be utilized to assess more in-depth clinical relevance and utility.

CONCLUSIONS

In the era of precision medicine and personalized spine care, understanding the “spinal phenotype profile” of individual patients is critical. This would allow better identification of the pain source for a more accurate diagnosis as well as aid in developing more precise clinical management algorithms that would ultimately

enhance patient outcomes and cost-effectiveness. It may also spur the development of novel regenerative therapies for discs or endplates and improve patient selection and outcomes for these treatments. This study's findings emphasize that the specific type of Modic change should not be dismissed and that it may be a vital MRI biomarker. We can conclude that Modic changes, particularly Modic type I/II, may have significant clinical relevance and represent a unique pathological process that demands attention by researchers and clinicians alike. Furthermore, Modic type I/II change is independently associated with pain profiles and might represent a unique underlying pathological process exhibiting more active endplate inflammation and pain generation. Our findings need to be explored further, and their impact upon clinical decision-making in patients who present with LBP should be evaluated. With innovations in machine learning and automated imaging, Modic changes can be a clinically relevant imaging phenotype that should be noted and mapped. In addition, our results underscore the importance of continued investigation of the molecular pathogenesis and genetics underlying Modic changes and the development of predictive models.

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Data Availability. All data generated from this research are presented in the manuscript and its accompanying figures and tables. Data generated from this research are available from the corresponding author upon reasonable request.

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